AMENDMENTS TO THE DRAWINGS

Replace FIG. 1 and FIG. 2 in the drawings as filed with the enclosed FIG. 1 and FIG. 2 replacement sheets.

REMARKS

Upon entry of the amendment, claims 5-12, 17-26, and 28-55 will be pending in the application. Claims 1-4, 13-16, and 27 are cancelled and claims 42-52 are withdrawn as drawn to non-elected inventions. Claims 5 and 28 are amended. Support for the amendments to the claims and for new claims 53-55 appears in, e.g., page 3, lines 1-7 and in the paragraph bridging pages 5 and 6. No new matter has been added by the amendments. Applicants reserve the right to pursue the subject matter of all cancelled and non-examined claims in a subsequent application or applications.

Applicants enclose replacement drawing sheets for FIGURES 1 and 2.

Rejections under 35 USC 112, first paragraph

Claims 1-4, 13-15, and 27 are rejected for overbreadth. (see paragraph numbered 1 on page 4 of the Office Action). These claims are cancelled with the present amendment. Therefore, this rejection can be withdrawn.

Claims 5-12, 16-26, and 28-41 are also rejected for overbreadth. (see paragraph numbered 2 on page 5 of the Office Action). The rejection is traversed to the extent it is applied to the claims as amended.

Independent claims 5 and 28, from which the remaining claims subject to the rejection depend, have been amended to specify that the recited polypeptide comprises the amino acid sequence of a human IL-11 polypeptide. The amino acid sequence of human IL-11 was well known in the art as of the Applicant's priority date (see, e.g, the paragraph bridging pages 5 and 6

of the specification), and Applicants submit that the full breadth of the invention now claimed can be practiced without undue experimentation.

Claims 1-26 and 36 are further rejected for overbreadth. (see paragraph numbered 3 on page 6 of the Office Action). Claims 1-4, 13-15 and 27 are cancelled. The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner asserts that the specification is not enabled for using a glidant other than talc in the recited formulations. Applicants respectfully disagree and submit that one of ordinary skill in the art could readily determine whether glidants in addition to talc could be used in the compositions and methods. Glidants are well-known in the art, and the specification provides concentrations and specific examples of two such glidants (talc and silicon oxide (Syloid)) at, e.g., page 2, lines 25-26; page 3, lines 21-25 and in the formulations shown in Tables 1, 5, 7, 9, and 10. Applicants request reconsideration and withdrawal of the rejection.

Claims 1-4, 13-15, and 17 are rejected for lack of written description. (see paragraph numbered 1 on page 7 of the Office Action). These claims are cancelled with the present amendment. Therefore, this rejection can be withdrawn.

Claims 5-12, 16-26, and 28-41 are rejected for lack of written description. (see paragraph numbered 2 on page 8 of the Office Action). The rejection is traversed to the extent it is applied to the claims as amended.

Claims 5 and 28, from which depend the remaining claims subject to the rejection, have been amended to specify that the recited IL-11 polypeptide has the amino acid sequence of a human IL-11. The amino acid sequence of human IL-11 was well known in the art as of the

priority date of Applicants' application (see, e.g., the paragraph bridging pages 5 and 6 of the specification). Applicants submit that it is not necessary to refer in the claims to an activity, source or amino acid composition for human IL-11 in order to satisfy the written description requirement. The Federal Circuit has recently stated that "[t]he 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge." (Capon v. Ether, Fed. Cir. 2005, No. 03-1480, -1481)." In Capon, the Federal Circuit ruled that the Board of Patent Appeals and Interferences erred in holding that generic claims drawn to chimeric antibody genes do not satisfy the written description requirement because the appellants' specifications did not reiterate the structure or formula or chemical name for the nucleotide sequence of the claimed genes. The court observed that "when the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh."

Similar to the appellants in Capon, Applicants' invention is not the discovery of IL-11 itself, whose identity and sequence has been known for many years. The currently claimed invention is instead based on new formulations of a polypeptide with the amino acid sequence of a human IL-11 polypeptide. Because one of ordinary skill in the art would readily know what is meant by Applicants' recitation of "IL-11" in the claims, Applicants submit it is not necessary to refer to structural or functional information to comply with the written description requirement.

Reconsideration and withdrawal of the rejection for lack of written description is requested.

Rejections under 35 USC 112, second paragraph

Claims 1-4 and 27 are rejected as indefinite. These claims are cancelled with the present amendment. Therefore, this rejection can be withdrawn.

Rejections under 35 USC 103

Claims 1-22, 25 and 27-41 are rejected as obvious in view of Savastano et al., US Patent No. 5,681,584 ("Savastano"). Claims 1-4, 13-15, and 27 are cancelled with the present amendment. The rejection is traversed to the extent it is applied to the remaining claims as amended.

Independent claim 5, from which depend claims 6-12, 16-21, and 25, and independent claim 28, from which depend claims 29-51, are drawn to a pharmaceutical composition that includes interleukin-11.

As noted by the Examiner, Savastano is silent with respect to including IL-11 in the claimed composition. (page 11, second paragraph). The Examiner nevertheless states:

> Savastano does disclose that the active agent can include polypeptides, such as interleukins. Because IL-11 is an interleukin, it would have been obvious to a trained artisan to incorporate IL-11 into the composition described by Savastano et al.

Applicants respectfully disagree. While the name assigned to IL-11 identifies this protein as a cytokine and interleukin, the properties of IL-11 distinguish it from other cytokines and interleukins. In particular, Savastano neither discloses nor suggests a formulation of a protein with IL-11's properties, i.e., a protein as basic and as insoluble is IL-11, nor does it

disclose or suggest a reasonable expectation of success in stabilizing such a protein.

IL-11 is not homologous to any known protein in any sequence database. Dr. Warne Declaration, paragraph 20.[1] Human IL-11 has no cysteines, no disulfide bonds, and no N-linked glycosylation sites. Dr. Warne Declaration, paragraph 20. The lack of these features dramatically decreases IL-11's solubility and stability characteristics. Dr. Warne Declaration, paragraph 20.

The lack of disulfide bonds and lack of N-linked glycosylation, make IL-11 an unusually distinctive protein. Disulfide bonds typically add much needed structural stability to proteins, increasing the thermal denaturation temperature and decreasing the potential for chemical denaturation. IL-11 has no disulfide bonds. Dr. Warne Declaration, paragraph 21. Glycosylation of a protein greatly enhances its solubility. IL-11 has no glycosylation. In contrast, IL-4 has three disulfide bonds and three N-linked glycosylation sites to which carbohydrate is attached. Dr. Warne Declaration, paragraph 22.

[1] The attached declaration of Nicholas Warne, a co-inventor of the present application, is a copy of a declaration submitted during prosecution of USSN 08/230,982, filed April 21, 1994, now issued as US Patent No. 6,217,732.

IL-11 also has a distinctively high leucine and arginine content. Dr. Warne Declaration, paragraphs 23-24. Most proteins are 5-10% leucine. IL-11 is 23% leucine (making the protein core extremely hydrophobic) and 10% arginine (making the protein extremely basic, pI ~ 12). This unusually high leucine content, of 23%, makes IL-11 more susceptible to precipitation and/or aggregation. Dr. Warne Declaration, paragraph 25. IL-11 precipitates upon thermal denaturation. In contrast, a cytokine like M-CSF remains soluble upon thermal denaturation. Dr. Warne Declaration, paragraph 25.

The unusually high leucine content, in combination with the unusually high arginine content, makes it impossible for one skilled in the art to predict such a protein's solubility characteristics, i.e., with leucine contributing to insolubility in contrast to charged arginine contributing to solubility. The unusually high arginine content and resultant extremely basic pI of IL-11 make it impossible to generalize solubility characteristics based on proteins that are not similarly basic. Dr. Warne Declaration, paragraph 26.

The above-discussion demonstrates that IL-11 has properties that distinguish it from other proteins, including cytokines and interleukins. In view of these properties, there is no expectation that constructing an IL-11 containing formulation with the formulations disclosed in Savastano would be successful. Applicants respectfully request reconsideration and withdrawal of the rejection for obviousness.

Claims 23, 24, and 26 are rejected as obvious over Savastano in view of Porter (Remington's Pharmaceutical Sciences, 19th Ed., 1995, Chapter 93, p. 1653, 1st col., 9th paragraph). Claims 23, 24 and 26 depend directly or indirectly from claim 5, which for the reasons described above is non-obvious over Savastano.

Obviousness-type Double Patenting

Claims 1-5, 13-20, 28-31, and 38-39 are provisionally rejected over claims 13, 15, 20, 22-23, 25 and 28 of USSSN 10/360,906 ("the '906 application").

Applicants note that the '906 application is not yet allowed and will address any double-patenting issues with respect to the claims pending in the present application and the claims in the '906 application upon the indication of allowable subject matter in the '906 application.

Please charge any additional fees that may be due, or apply any credit for same, to Deposit Account No. 50-0311(Reference No. 22058-544).

Respectfully submitted,

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Ivor R. Elrifi, Reg. No. 39,529
David E. Johnson, Reg. No. 41,874
Attorneys for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623

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